



Technical Reports

Trip Report for
“Advances in Synthetic and Medicinal Chemistry”

St. Petersburg, Russia
August 27-31, 2007

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Abstract: *International Symposium “Advances in Synthetic and Medicinal Chemistry” was held in St. Petersburg, Russia, August 27-31, 2007. This conference was organized by the European Federation of Medicinal Chemistry and sponsored by Cambridge Corporation. The conference included a total of 15 plenary lectures, 31 short talks, and oral communications and a poster session.*

“The Changing Face of Organic Synthesis”

Steven V. Ley

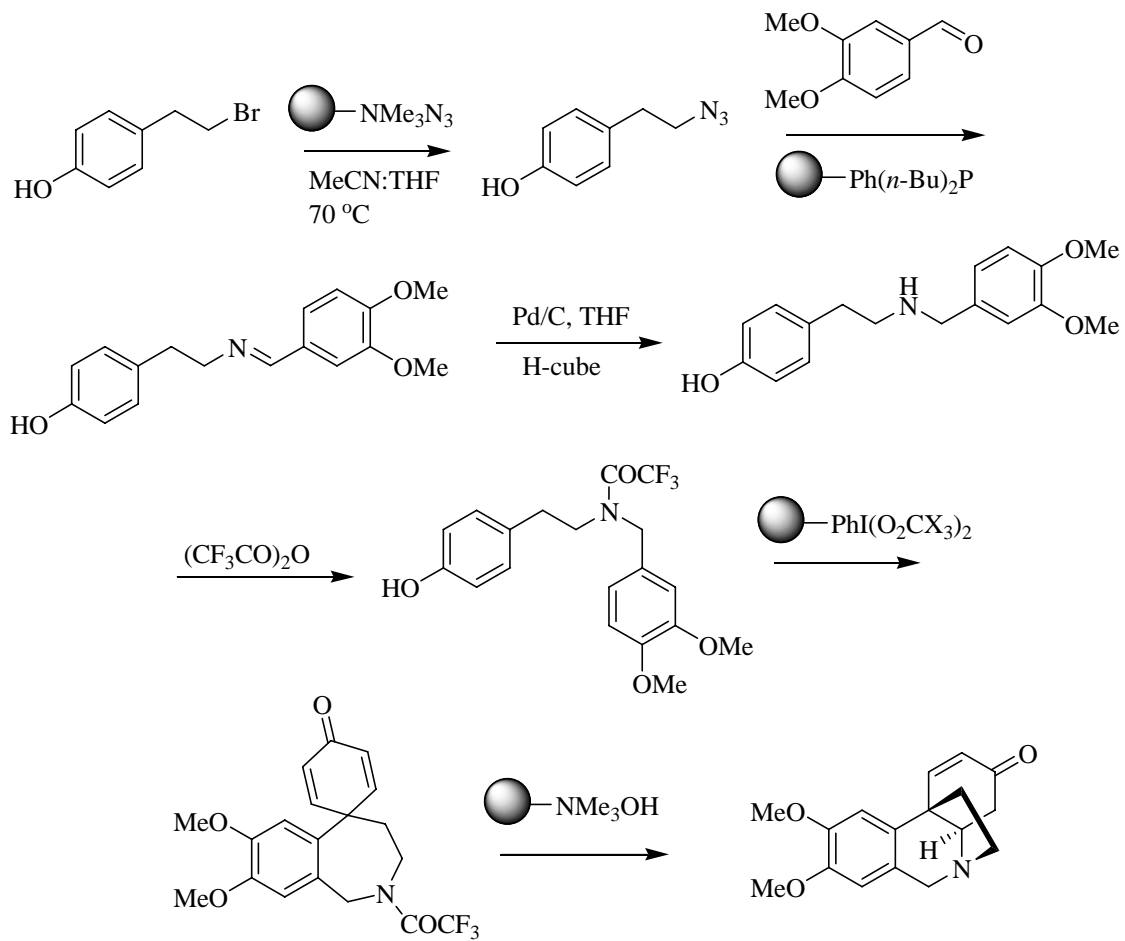
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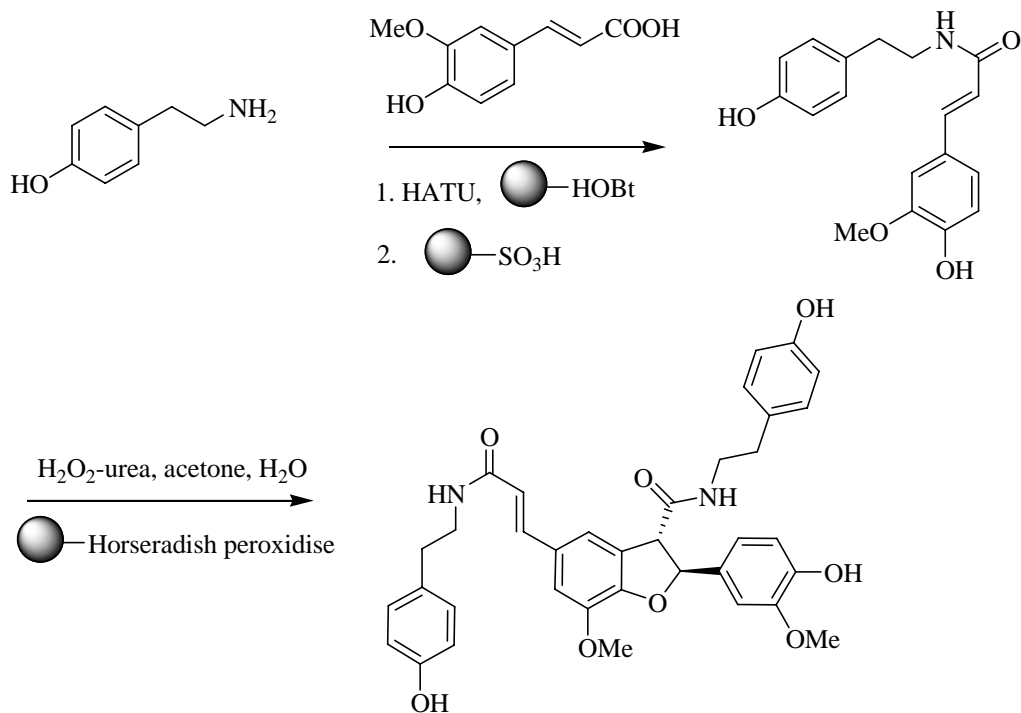
The search for new ways to assemble molecules continues to be an important driver for organic synthesis. The biological activity and exquisite structural diversity of many natural products stimulates invention by challenging today's synthetic methodology. However, preparing such materials from small and commercially available building blocks inevitably involves multiple synthetic steps. For most modern drugs and other complex molecules, it is not uncommon for syntheses to require at least 10 steps, and sometimes many more.

The combination of advanced scavenging agents and catch-and-release techniques with the use of continuous flow processing was reported to create even greater opportunities for organic synthesis. As important examples of these developments, we have recently completed the syntheses of the natural products oxomaritidine (Scheme 1) and grossamide (Scheme 2) entirely by using these flow chemistry methods. The syntheses required the construction of a fully automated continuous flow reactor system (using a simple pumping arrangement) with immobilized reagents packed in columns to effect the synthesis steps efficiently. These examples illustrate the rapid and flexible nature of the methods for preparing compounds on demand and at various scales. The future vision of this emerging field could well cause a paradigm shift in the way chemical synthesis is conducted.

Scheme 1



Scheme 2

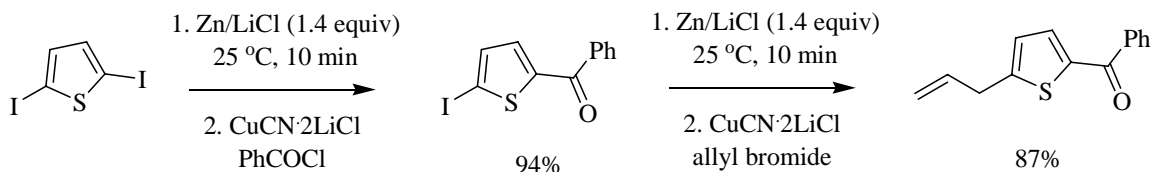


“Functionalized Mg And Zn Reagents for The Synthesis of Highly Functionalized Aromatics and Heterocycles”

Prof. Paul Knochel, Ludwig Maximilians University of Munich, Germany

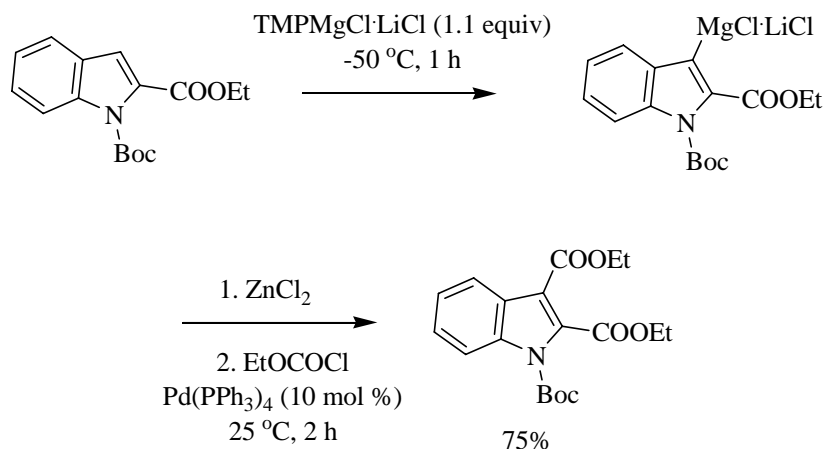
In the first part of the lecture, the preparation of highly functionalized organozinc compounds was emphasized using zinc powder in the presence of LiCl. This method allows the preparation of a range of heteroarylzinc species bearing a ketone or an aldehyde (Scheme 3).

Scheme 3



In a second part, the preparation of polyfunctional magnesiated heterocycles using either a X/Mg- exchange triggered by *i*-PrMgCl-LiCl or by a direct deprotonation using new soluble Mg-bases such as TMPMgCl-LiCl or (TMP)₂Mg-2LiCl (Scheme 4).

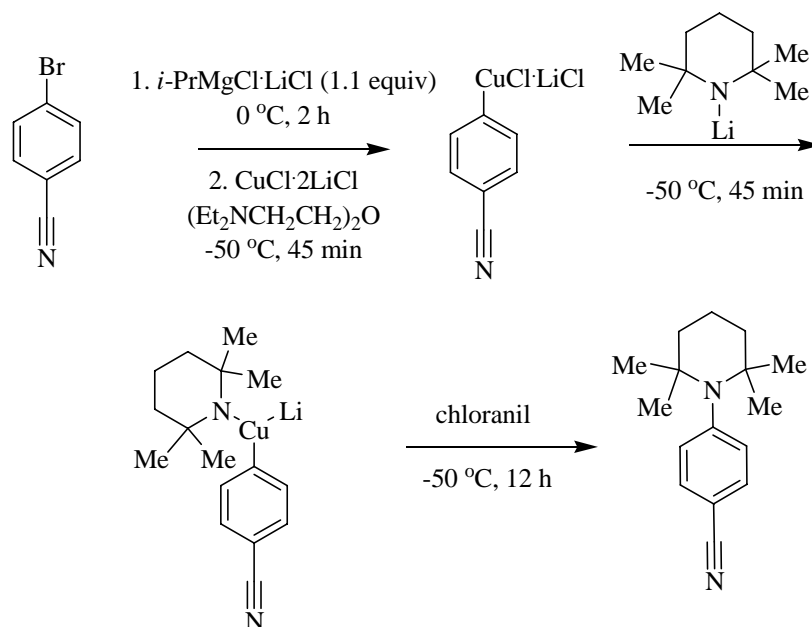
Scheme 4



The new mixed Mg/Li-bases of the general type $\text{R}_2\text{NMgCl}\cdot\text{LiCl}$ which have a high kinetic activity because of the presence of LiCl which breaks up oligomeric aggregates of magnesium amides were reported. The use of $\text{TMPMgCl}\cdot\text{LiCl}$, which has an excellent solubility and is stable for more than 6 months as THF solution at $25\text{ }^\circ\text{C}$, allows the regioselective functionalization of various aromatic and heteroaromatic compounds. It provides access to new magnesium species not readily available by Br/Mg-exchange reactions or previously reported metalation procedures. Applications of these polyfunctional organometallics for the synthesis of bioactive molecules have been shown.

The synthesis of aminated heterocycles using an oxidative amination procedure with chloranil was also described (Scheme 5).

Scheme 5



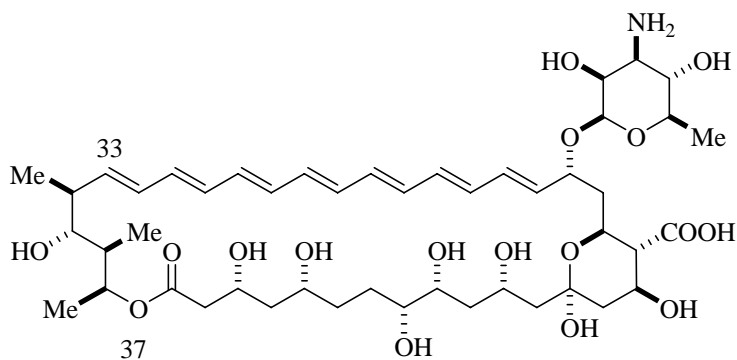
“Surprises and Discoveries with Natural Products”

Erick M. Carreira

ETH-Zürich, Laboratorium für Organische Chemie, ETH Hönggerberg
Switzerland

In the first part of the lecture studies of Amphotericin B (AmB, Figure 1), one of the most prominent members of the polyene macrolide antibiotics were discussed. AmB serves as the drug of choice in the clinic for antifungal chemotherapy in life-threatening infections, although it is poorly tolerated and elicits adverse side effects. With a rising number of fungal infections resistant to extant remedies, the development of analogs with improved therapeutic profiles has become increasingly necessary. Additionally, because the mechanism of action of amphotericin and its toxicity are not yet fully understood, efficient synthesis strategies allow access to active structures that serve as designed probes, providing insight into the mode of action of these remarkable natural products.

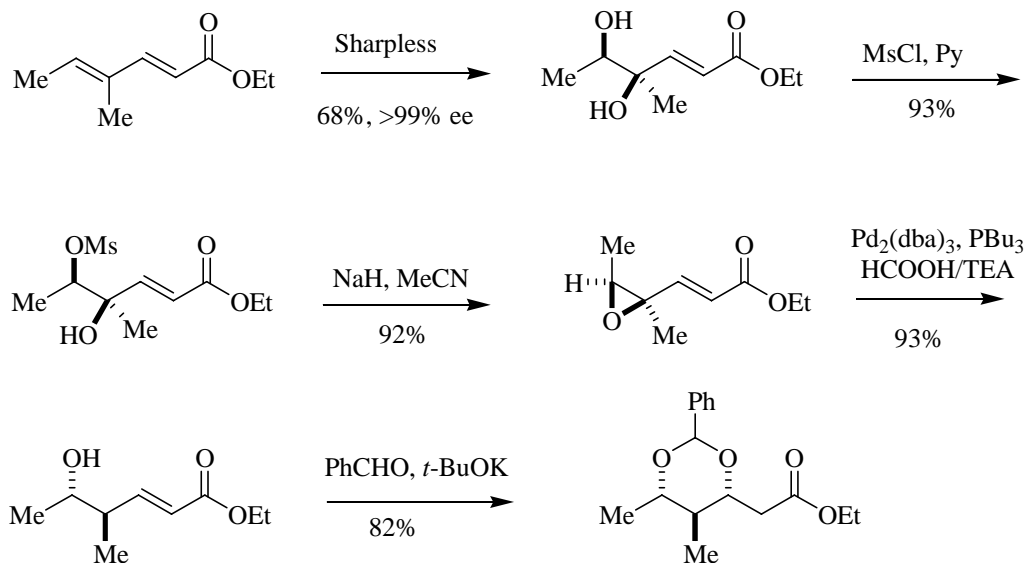
Figure 1



An expeditious, efficient, asymmetric synthesis of the C(33)-C(37) fragment of amphotericin B that proceeds in 14 steps and 16% overall yield from *E*-2-methylbut-2-enal with complete stereocontrol was described. The route (Schemes 6 and 7) relies on the application of recently developed methods in catalytic asymmetric synthesis for stereocontrol through enantio- and diastereoselective functionalization of a substituted sorbate derivative.

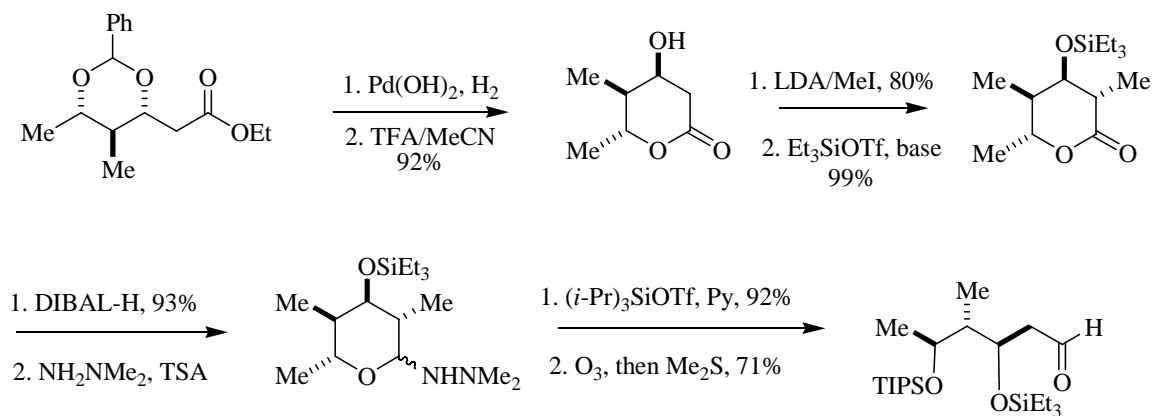
Synthesis starts with methyl substituted derivative of ethyl sorbate and results after five steps in protected 1,3-diol (Scheme 6).

Scheme 6



The following steps resulted in the final aldehyde as single isomer without any observed epimerization at the future C(34) center.

Scheme 7



“Smiles Rearrangement and Isocyanide Chemistry”

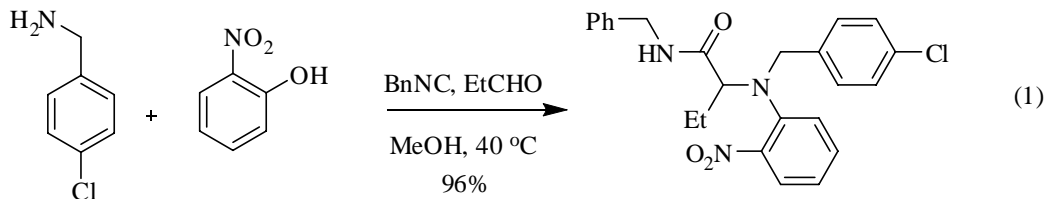
L. Grimaud, L. El Kaïm, J. Oble, M. Gizolme

Unité Chimie et Procédés, Ecole Nationale Supérieure Des Techniques Avancées

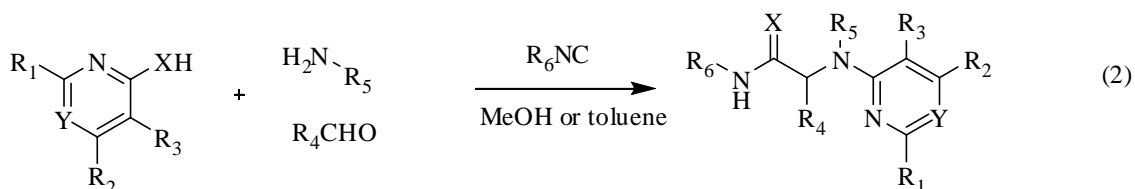
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The talk described a novel four component coupling based on isocyanide chemistry using electron-deficient phenols instead of carboxylic acids classically used in Ugi reactions (Equation 1). The final Smiles rearrangement constitutes the key step of this new process allowing an efficient coupling of a primary amine with an isocyanide, a carbonyl

compound and a properly substituted phenol. Moreover, the same concept can be applied to the analogous Passerini reaction.



The potential of this new multi-component coupling was further extended using heterocyclic phenols as well as heterocyclic mercapto derivatives (Equation 2). This strategy affords a new and direct route to biologically relevant heterocyclic scaffolds.



The combination of multicomponent reactions with post-condensation transformations offers the ability to introduce even more complexity in the generated scaffolds. As an example, a rapid access to pyrimido azepine scaffolds was proposed by using an Ugi-Smiles/RCM sequence (Scheme 8).

Scheme 8

